

CONDYLOX - podofilox gel

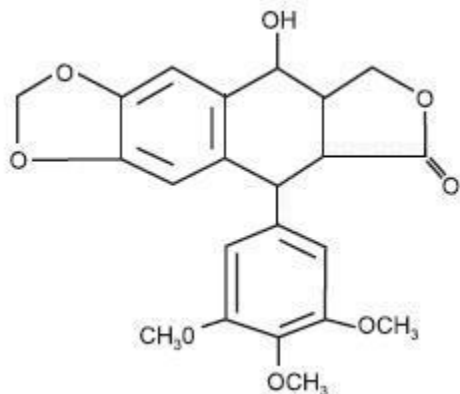
Watson Pharmaceuticals, Inc.

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DESCRIPTION

Podofilox is an antimitotic drug which can be chemically synthesized or purified from the plant families *Coniferae* and *Berberidaceae* (e.g. species of *Juniperus* and *Podophyllum*). Condylox Gel 0.5% is formulated for topical administration. Each gram of gel contains 5 mg of podofilox in a buffered alcoholic gel containing alcohol, glycerin, lactic acid, hydroxypropyl cellulose, sodium lactate, and butylated hydroxytoluene.

Podofilox has a molecular weight of 414.4 daltons, and is soluble in alcohol and sparingly soluble in water. Its chemical name is [5R, -(5 α , 5a β , 8a α , 9 α)]-5,8,8a,9-tetrahydro-9-hydroxy-5-(3,4,5-trimethoxyphenyl) furo[3',4':6,7]naphtho-[2,3,-d]-1,3-dioxol-6(5aH)-one. Podofilox has the following structural formula:



CLINICAL PHARMACOLOGY

Mechanism of Action

Treatment of anogenital warts with podofilox results in necrosis of visible wart tissue. The exact mechanism of action is unknown.

Pharmacokinetics

In systemic absorption studies in 52 patients, topical application of 0.05 mL of an ethanolic solution containing 0.5% podofilox to external genitalia did not result in detectable serum levels. Applications of 0.1 to 1.5 mL resulted in peak serum levels of 1 to 17 ng/mL one to two hours after application. The elimination half-life ranged from 1.0 to 4.5 hours. The drug was not found to accumulate after multiple treatments¹.

CLINICAL STUDIES

In the first multicenter clinical study in 326 patients with anogenital warts, Condylox Gel 0.5% and its vehicle were applied in a double-blind fashion to comparable patient groups. Of the 260 patients with efficacy data, 176 were treated with Condylox Gel 0.5%. Patients applied Condylox Gel 0.5% twice daily for three consecutive days followed by a 4 day "rest" period.

At the end of 4 weeks, 38.4% of the patients had complete clearing of the wart tissue when treated with Condylox Gel 0.5%.

In the second multicenter clinical trial in 108 evaluable patients with anogenital warts, Condylox (podofilox) Topical Solution 0.5% was compared with Condylox Gel 0.5% for efficacy. As in the first clinical trial, patients applied Condylox Gel 0.5% twice daily for three consecutive days followed by a four day "rest" period.

Similar clearance rates were observed. At the end of 4 weeks, 25.6% of the patients had complete clearing of the wart tissue when treated with Condylox Gel 0.5%.

INDICATIONS AND USAGE

Condylox Gel 0.5% is indicated for the topical treatment of anogenital warts (external genital warts and perianal warts). This product is *not* indicated in the treatment of mucous membrane warts (see **PRECAUTIONS**).

Diagnosis

Although anogenital warts have a characteristic appearance, histopathologic confirmation should be obtained if there is any doubt of the diagnosis. Differentiating warts from squamous cell carcinoma and "Bowenoid papulosis" is of particular concern. Squamous cell carcinoma may also be associated with human papillomavirus which should not be treated with Condylox Gel 0.5%.

CONTRAINDICATIONS

Condylox Gel 0.5% is contraindicated for patients who develop hypersensitivity or intolerance to any components of the formulation.

WARNINGS

Correct diagnosis of the lesions to be treated is essential. See the **Diagnosis** subsection of the **INDICATIONS AND USAGE** section. Condylox Gel 0.5% is intended for cutaneous use only. **Avoid contact with the eyes. If contact with the eyes occurs, patients should immediately flush the eyes with copious quantities of water and seek medical advice.**

Drug Product is Flammable.

Keep Away From Open Flame.

PRECAUTIONS

General

Data are not available on the safe and effective use of this product for treatment of warts occurring on mucous membranes of the genital area (including the urethra, rectum and vagina). The recommended method of application, frequency of application, and duration of usage should not be exceeded (see **DOSAGE AND ADMINISTRATION**).

Information for Patients

Patients using Condylox Gel 0.5% should receive the following information and instructions. This information is intended to aid in the safe and effective use of this medication. It is not intended to disclose all possible adverse or intended effects.

1. This medication should be used only as directed by the health care provider. Patients should be instructed to wash their hands thoroughly before and after each application. It is for external use only. Avoid contact with the eyes.
2. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
3. Patients should report any signs of adverse reactions to the health care provider.
4. If no improvement is observed after 4 weeks of treatment, discontinue the medication and consult the health care provider.

Carcinogenesis, Mutagenesis and Impairment of Fertility

An 80-week carcinogenicity study in the mouse was performed using a 0.5% podofilox solution applied dermally at 0.04, 0.2 and 1.0 mg/kg/day. There were no differences between the podofilox treated mice at any dose level and vehicle control in the incidence of neoplasia. Published animal studies, in general, have not shown the drug substance, podofilox, to be carcinogenic.^{2,3,4,5,6} There are published reports that, in mouse studies, crude podophyllin resin (containing podofilox) applied topically to the cervix produced changes resembling carcinoma *in situ*.⁷ These changes were reversible at five weeks after cessation of treatment. In one reported experiment, epidermal carcinoma of the vagina and cervix was found in 1 out of 18 mice after 120 applications of podophyllin⁸ (the drug was applied twice weekly over a 15-month period).

Podofilox was not mutagenic in the Ames plate reverse mutation assay at concentrations up to 5 mg/plate, with and without metabolic activation. No cell transformation related to potential oncogenicity was observed in BALB/3T3 cells after exposure to podofilox at concentrations up to 0.008 µg/mL, without metabolic activation and 12 µg/mL podofilox with metabolic activation. Results from the mouse micronucleus *in vivo* assay using podofilox 0.5% solution at doses up to 25 mg/kg (75 mg/m²), indicate that podofilox should be considered a potential clastogen (a chemical that induces disruption and breakage of chromosomes).

Daily topical application of 0.5% podofilox solution at doses up to the equivalent of 0.2 mg/kg (1.18 mg/m², approximately equivalent to the human daily dose) to rats throughout gametogenesis, mating, gestation, parturition and lactation for two generations demonstrated no impairment of fertility.

Pregnancy

Pregnancy Category C: 0.5% podofilox solution was not teratogenic in the rabbit following topical application of up to 0.21 mg/kg (2.85 mg/m², approximately 2 times the maximum human dose) once daily for 13 days. The scientific literature contains references that podofilox is embryotoxic in rats when administered intraperitoneally at a dose of 5 mg/kg (29.5 mg/m², approximately 19 times the recommended maximum human dose).⁹ Teratogenicity and embryotoxicity have not been studied with intravaginal application. Many antimitotic drug products are known to be embryotoxic. There are no adequate and well-controlled studies in pregnant women. Condylox Gel 0.5% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from podofilox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

In clinical trials with Condyllox Gel 0.5%, the following local adverse reactions were reported during the treatment of anogenital warts. The severity of local adverse reactions were predominantly mild or moderate and did not increase during the treatment period. Severe reactions were most frequent within the first 2 weeks of treatment.

| Adverse Reaction | Mild | Moderate | Severe |
|------------------|-------|----------|--------|
| Inflammation | 32.2% | 30.4% | 9.3% |
| Burning | 37.1% | 25.9% | 11.5% |
| Erosion | 27.0% | 20.8% | 8.9% |
| Pain | 23.7% | 20.4% | 11.5% |
| Itching | 32.2% | 16.0% | 7.8% |
| Bleeding | 19.2% | 3.0% | 0.7% |

Other local adverse reactions reported included stinging (7%), and erythema (5%); less commonly reported local adverse events included desquamation, scabbing, discoloration, tenderness, dryness, crusting, fissures, soreness, ulceration, swelling/edema, tingling, rash, and blisters.

The most common systemic adverse event reported during the clinical studies was headache (7%).

OVERDOSAGE

Topically applied podofilox may be absorbed systemically (see **CLINICAL PHARMACOLOGY** section). Toxicity reported following systemic administration of podofilox in investigational use for cancer treatment included: nausea, vomiting, fever, diarrhea, bone marrow depression, and oral ulcers. Following 5 to 10 daily intravenous doses of 0.5 to 1 mg/kg/day, significant hematological toxicity occurred but was reversible.¹⁰ Other toxicities occurred at lower doses. Toxicity reported following systemic administration of podophyllum resin included: nausea, vomiting, fever, diarrhea, peripheral neuropathy, altered mental status, lethargy, coma, tachypnea, respiratory failure, leukocytosis, pancytosis, hematuria, renal failure and seizures.¹¹ Treatment of topical overdosage should include washing the skin free of any remaining drug and symptomatic and supportive therapy.

DOSAGE AND ADMINISTRATION

The prescriber should ensure that the patient is fully aware of the correct method of therapy and identify which specific warts should be treated.

Apply twice daily for 3 consecutive days, then discontinue for 4 consecutive days. This one week cycle of treatment may be repeated until there is no visible wart tissue or for a maximum of four cycles. **If there is incomplete response after four treatment cycles, discontinue treatment and consider alternative treatment. Safety and effectiveness of more than four treatment cycles has not been established.** There is no evidence to suggest that more frequent application will increase efficacy, but additional applications would be expected to increase the rate of local adverse reactions and systemic absorption.

Condyllox Gel 0.5% should be applied to the warts with the applicator tip or finger. Application on the surrounding normal tissue should be minimized. **Treatment should be limited to 10 cm² or less of wart tissue and to no more than 0.5 g of the gel per day.** Care should be taken to allow the gel to dry before allowing the return of opposing skin surfaces to their normal positions. Patients should be instructed to wash their hands thoroughly before and after each application.

HOW SUPPLIED

Condyllox Gel 0.5% is supplied as 3.5 g of clear gel in aluminum tubes with an applicator tip. NDC 52544-045-13. Store at controlled room temperature between 15 - 30°C (59 - 86°F). **Avoid excessive heat. Do not freeze.**

Keep out of reach of children.

Rx only

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